CLINICAL PROCEEDINGS

of the

CHILDREN'S HOSPITAL

WASHINGTON, D. C.

August 1953

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OF THE CHILDREN'S HOSPITAL

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INFECTIOUS (EPIDEMIC) HEPATITIS IN INFANCY AND CHILDHOOD*

Special Report No. 269

Jesse W. Nudelman, M.D.

INTRODUCTION

The increasing frequency of sporadic epidemic infectious hepatitis in infants and children and a consequent renewed interest in the subject by doctors who care for children has prompted the present review of the etiology, epidemiology, and clinical manifestations of the disease, together with the record of two cases.

ETIOLOGY AND EPIDEMIOLOGY

Although infectious hepatitis has long been recognized in civilian and military personnel, the modern concept of its viral etiology is a product of World War II investigators. Voegt in 1942 was the first to report transmission of the disease to human volunteers. Subsequently others demonstrated an infectious agent in the blood and stools of patients in the acute phase of the disease.

Infectious hepatitis is a primary disease of childhood in the civilian population although it can occur at any age. Highest attack rates occur in the 10–14 year age group and the disease is uncommon under five years. In an epidemic in a town of 3800 inhabitants, the attack rate was 6.0 per 1000 for the total population compared to the rate of 54.5 per 1000 for school children. The disease may occur at any season of the year. However, there is a seasonal trend toward increased incidence during late winter and early spring. Sex is not a factor in susceptibility to this virus. There appears to be a relative immunity to infectious hepatitis among the dark-skinned races as noted in the Negro troops during World War II.

The incubation period is 14–40 days. In most cases it is between 18 and 30 days, although a period as long as 85 days has been noted. This incubation period contrasts with that of homologous serum hepatitis which approximates from 60–135 days. Although epidemic spread of infectious hepatitis is common, it does not occur with homologous serum hepatitis.

There is suggestive evidence that patients with chronic infection continue to be sources of contagion and that the virus of infectious hepatitis may be present in feces up to 15 months after the onset of symptoms.

* Acknowledgment is made of the assistance of Dr. Timothy Tehan, USNR, and Dr. Robert Parrott, National Institutes of Health, in the preparation of this article. A portion of this paper was read at a monthly staff conference in June, 1952, at St. Catherine's Hospital, Brooklyn, New York.

Transmission

Numerous attempts to produce infectious hepatitis by transmitting the virus to laboratory animals, including rodents and many species of monkeys and chimpanzees, have failed. Successful transmission of virus to pigs, canaries, embryonated eggs, and rats has been reported but not confirmed.

In human beings, experimental studies have shown that the virus of infectious hepatitis may be acquired by oral ingestion or parenteral injection. One strain of infectious hepatitis virus in serum is highly effective in inducing hepatitis when administered orally to volunteers. It is relatively ineffective in inducing this disease when administered parenterally to normal persons. Virus of infectious hepatitis is frequently present in the feces of persons with active disease and causes the disease in normal persons when it enters by the oral route. Urine from patients with infectious hepatitis has been administered by oral inoculation and did not produce this disease in human volunteers.

The seasonal trend of this disease favors a respiratory means of transmission but attempts to demonstrate the virus in nasopharyngeal washings obtained from patients during the pre-icteric and icteric stages of the disease, with one possible exception, have been unsuccessful.

Contaminated articles, including drinking water, milk, other foods, personal contact and flies are highly probable sources of transmission of virus. An important epidemiologic factor is that children between six and 10 months of age play together and since they are not toilet trained, fecal contamination of bodies, clothing and bed linen is common.

Immunity and Susceptibility

There is experimental evidence of an antigenic similarity between two strains of infectious hepatitis virus isolated in Pennsylvania and Sicily. Several authors have noted a resistance to reinfection with infectious hepatitis virus during the first year after infection. There is evidence indicating existence of homologous immunity but an absence of cross immunity in patients with infectious and serum hepatitis.

A large percentage of newborn infants may be protected against infectious hepatitis for periods up to six months by placentally transmitted maternal antibodies. Gamma globulin in a dosage of 0.01 cc. per pound of body weight has been effective in preventing or modifying hepatitis. This must be given five to seven days prior to onset of jaundice.

Epidemics

Outbreaks of infectious hepatitis have been recognized for at least 200 years. Although they are particularly extensive among armies in the field, civilian epidemics have also frequently been encountered.

An epidemic reported recently occurred in an orphanage for infants and small children under three years of age. The average census was 200, of whom 50 individuals were student nurses. The remainder were children, one third of whom were over one year of age and two-thirds of whom were younger. In the three-year period during which this epidemic flourished the incidence of acute hepatitis with jaundice among the student nurses was 32 per cent. With the use of gamma globulin or aseptic technique, cases of infectious hepatitis no longer occurred in student nurses.

During a concomitant 18 month period, 42 cases of infectious hepatitis were diagnosed in infants. Only those cases were reported in which at least three different liver function tests were positive and the clinical findings were consistent with liver disease. An attempt was made to confirm the clinical diagnosis by means of a skin test. According to the skin test 80 per cent of children remaining in the institution for over six months had been infected with this virus. Jaundice or hyperbilirubinemia was observed in only one of the 42 clinically recognized cases. Clearly then, the disease in the children was almost entirely of the non-icteric variety. These data also indicated that in this institution the disease was quite contagious among infants.

CLINICAL SIGNS AND SYMPTOMS

The clinical manifestations and laboratory findings in cases of infectious hepatitis vary with the age of the patient. Well recognizable clinical findings and/or abnormal hepatic function tests may not be present.

During infancy the usual clinical findings are those of anorexia, malaise, restlessness, vomiting and diarrhea, usually of 3 to 14 days duration. Icterus is *not* common.

In children the symptoms of an upper respiratory infection are common and have been found in 75 per cent of patients under 12 years of age. This incidence of respiratory symptoms gradually declines to between 17 and 50 per cent as puberty and adulthood are reached. Abdominal pain, colicky or continuous in nature, is intense and common. Nausea and vomiting occur in from 70 to 90 per cent of patients while diarrhea occurs less frequently as the child grows older. In the epidemics studied, the impression was that between 20 and 30 per cent of those infected were non-icteric. Routine liver function tests showed a high percentage of abnormal findings in the age group beyond infancy.

RELIABILITY OF LABORATORY STUDIES

Routine laboratory hepatic function tests made on some normal infants during the first six weeks may give abnormal findings. It is suggested that the one-minute bilirubin, the thymol turbidity and the cephalin-cholesterol

flocculation tests be used as satisfactory aids to accurate laboratory diagnosis in this age group. Urobilinogen may not be found in normal newborn infants' urine because of the absence of appropriate intestinal flora to reduce bilirubin to urobilinogen. The usual liver function tests are more reliable beyond the period of infancy.

MORBIDITY AND MORTALITY

Although infectious hepatitis is considered to be a benign disease, it is probably too early to know the incidence of chronicity and its residual effects. Traisman summarized by saying "contrary to the general belief, our experience suggests that although this condition is uncommon in infancy, the prognosis is much more serious than in older children."

PREVENTION OF EPIDEMICS

The prevention of the epidemic spread of infectious hepatitis is based upon the following considerations:

1. The early diagnosis of the non-icteric cases. It is possible that the skin test, if developed for general use, may be a valuable screening method of diagnosis before chemical and hepatic function tests are performed.
2. Isolation precautions must be based on the assumption that the contagious period begins with the onset of symptoms and lasts until the clinical recovery has occurred. It must be remembered that a carrier state may exist as the virus may be found in the stool for many months.
3. Aseptic technique is indicated in handling patients to prevent the perpetuation of disease by contamination of clothes, bed linen, bodies and possible parenteral transmission by syringes and needles.
4. Fecal contamination of water, milk, food products and flies may be an important factor.
5. Gamma globulin can be used to modify or prevent this disease.

CASE PRESENTATION

Two cases of infectious hepatitis in children are presented to illustrate the typical and atypical forms: the first, a child, with known contact; the second, an infant with an atypical clinical and laboratory course.

*Case No. 1**

This seven and a half year-old white female had been well until six days prior to hospital admission in May 1953 because of abdominal pain and fever. Vomiting, anorexia and lassitude had been noted. The urine had been dark in color and a whitish stool was noted just prior to admission. There was no history of jaundice, rash or pruritis. The child had pneumonia in October 1952, and chicken pox early in 1953.

* A staff case from Dr. Preston McLendon's service at the Children's Hospital, Washington, D. C.

She was the only child and the parents had been well. The patient had been attending school where a known epidemic of infectious hepatitis had occurred during the school year.

Physical examination showed an asthenic, undernourished, and chronically ill white female, not jaundiced and not in acute distress. The temperature was 100 degrees F. Positive physical findings included a scaphoid abdomen with firm, tender liver that extended 3 centimeters below the right costal margin. Inguinal and axillary lymph nodes were palpable.

Pertinent laboratory studies included a thymol turbidity of 6.8 units on admission and 12.2 units four days later, and a cephalin flocculation which was negative on admission but was 2+ at 48 hours on the fourth hospital day. The total bilirubin was 1.24 mgm/100 ml; prompt direct, 0.64 mgm and indirect, 0.60 mgm.

Urinalysis was within normal limits. The peripheral blood count showed a leukopenia with a relative lymphocytosis.

*Case No. 2**

This five-week-old white female infant was admitted to the Hospital in April 1952, with the following symptoms: occasional vomiting of one week's duration changing to vomiting after each meal for three days before admission; jaundice of three days' duration and irritability. The diet consisted of breast milk. No vitamin supplements were given. The bowel movements were irregular and stools changed from a normal yellow pasty consistency to a green seedy nature. No accurate knowledge of the infant's temperature was available. The infant was born of a normal, low forcep, full gestational delivery. Birth weight was 5 pounds 6 ounces. The newborn hospital stay was uneventful. Normal stools and only slight icterus were reported prior to discharge. Between the time of discharge and readmission, the infant had no contact with a person with infectious hepatitis and is said to have been well. She was the first child of parents born in Italy. There is no familial history of jaundice or recent illness.

On physical examination this five week-old female was jaundiced, irritable and poorly nourished but satisfactorily hydrated with no evidence of generalized lymphadenopathy. Her weight was 8 pounds 6 ounces and temperature 99 degrees. Skin turgor was poor, skin and sclera were icteric. The abdomen was distended, soft and non-tender. The liver was palpable 2.5 centimeters below the right costal margin and the spleen 2 centimeters below the left costal margin. No other abdominal mass was felt and the remainder of the physical examination was normal.

Hemogram on admission was normal but the infant gradually became anemic and required a transfusion. A normal white blood count was recorded on admission, but over a two-week period leukopenia with relative lymphocytosis developed.

The patient's sedimentation rate, reticulocyte count, prothrombin time, bleeding and coagulation time, platelet count and red blood cell fragility were all within normal limits. Blood cultures were negative.

The stools were positive for bile but negative for urobilinogen at the onset but one month after admission a small amount of urobilinogen was recorded. Urinalysis revealed bile in all specimens but urobilinogen or urobilin were never recorded prior to final diagnosis.

Extensive blood chemical, hepatic function and hematological examination did

* A staff case from Dr. Philip J. Lombardi's service at St. Catherine's Hospital, Brooklyn, New York.

not aid toward the diagnosis. In fact, the qualitative bilirubin suggested obstructive jaundice.

The infant's weight varied during a six week period from 8 pounds 6 ounces to 7 pounds 7 ounces, and thereafter the patient continued to gain. During hospitalization jaundice became more pronounced, gradually assuming a greenish yellow tint. The stools became lighter in color but were not acholic. The liver and spleen slowly but progressively increased in size and the clinical picture became worse for about one month, after which the clinical picture improved while the patient was on conservative therapy, and soon became stationary. A liver biopsy was performed with histological findings indicative of infectious hepatitis.

SUMMARY

The etiology, epidemiology and clinical manifestations of infectious hepatitis have been reviewed. Two cases of infectious hepatitis have been presented and an epidemic cited to illustrate the mode of transmission of this disease. Suggestions are offered to prevent the spread of infectious hepatitis.

N.B.: Because of space limitations and the large volume of references, the editors have omitted publication of the bibliography.

CYST AND CYST-LIKE LESIONS OF THE LUNG

Special Report No. 270

Sidney Rosenbaum, M.D.
Joseph Giardino, M.D.

INTRODUCTION

In the past few years several reports have appeared in the literature dealing with the occurrence of cyst and cyst-like lesions in the lung and pleural space. We have reviewed the cases in Children's Hospital and have chosen the following as an example of our experience and that to be encountered in an institution of this size.

CASE PRESENTATION

Case No. 1

C. M., a three-month-old colored male, was admitted to Children's Hospital on October 29, 1952, with a history of an upper respiratory infection characterized by sneezing and coryza. In addition the patient had a non-productive cough which was persistent, and a temperature of 104 F. He was treated in the clinic with one injection of penicillin but the condition persisted. When the child developed respiratory distress he was admitted to this hospital.

Physical examination revealed a well developed colored male infant weighing

13¾ pounds, with a temperature of 103 F. rectally, pulse rate of 130 per minute and respirations 80 per minute. Positive findings consisted of flaring of the ala nasi, moderate injection of the pharynx, and infracostal retraction. There was dullness as well as diminished breath sounds throughout the right lung field.

Hemogram on admission disclosed 9.5 grams of hemoglobin, white blood cell count 17,700 with a differential of 27 per cent segmented polymorphonuclear leukocytes, 10 band forms and 2 young forms, 60 per cent lymphocytes, 1 monocyte, and normal platelets. Hematocrit was 33 per cent. Results of urinalysis were negative and blood culture was negative. The child was placed in an oxygen tent and given 600,000 units of S.R. penicillin, and 100 milligrams of aureomycin every 24 hours.

The initial roentgenogram was made on October 29, 1952, and revealed multiple loculated areas of decreased density surrounded by zones of fibrosis and pleural thickening overlying the fluid level in the eighth interspace posteriorly. The size of the translucent areas varied. One "cystic" area became sufficiently large so as to herniate through the mediastinum.

The remainder of the clinical course was characterized by return to a normal status. The child became afebrile after one week of therapy, and was removed from the oxygen tent on November 8, 1952; from that time until he was discharged there was no evidence of respiratory distress, although the rate of respiration was increased even while the patient was asleep. At the time of discharge to a convalescent home, the patient appeared to be a normal infant who was alert, responsive and well developed, with physical signs of diminished aeration in the right lung field. Three months later, his condition was reported as satisfactory.

Case No. 2

R. M., a two-month-old white female, was admitted to the Children's Hospital on September 12, 1952, with a history of a "cold" for one week prior to admission. A physical examination disclosed no abnormalities. One parenteral dose of penicillin was administered. There was no change in condition until one day before admission to the Children's Hospital when she became feverish and began to cough. Past medical history and family history were essentially negative.

Examination revealed a well-developed infant with a mucopurulent nasal discharge. The respiratory rate was 80 per minute. The chest was dull on percussion and bronchial breathing with fine rales were heard over the left lower lobe.

A hypochromic anemia (2 nucleated red blood cells per 100 white blood cells) with a leukocyte count of 24,000 and a differential of 73 segmented cells, 9 band forms 5 young forms, 12 lymphocytes, and 1 monocyte was found.

Combiotic was administered initially followed by 50 milligrams of chloromycetin palmitate every 4 hours for 3 days, and 300,000 units of aqueous penicillin every 24 hours for 4 days. The patient was placed in an oxygen tent for 7 days.

The illness was characterized by respiratory difficulty, marked nasal discharge, sneezing with dullness in the right chest, diminished breath sounds, and rales.

Roentgenograms of the chest first taken on September 22, 1952, revealed an opacity involving the lower half of the right chest, above which was a circumscribed area of essentially normal tissue. Above this area the apex of the lung appeared to be clear. This was interpreted roentgenologically as representing loculated fluid or a large abscess. A consultant interpreted the film as indicating a lung cyst with fluid level, or segmental obstructive emphysema secondary to a pneumonic process. Further observation was advised. Later the true nature of the lesion was revealed. On September 25, roentgen examination revealed a circumscribed area measuring about 5

centimeters in diameter, the upper half showing rarifaction, the lower half apparently containing fluid.

The patient was discharged on September 27, 1952, apparently in good condition, there being persistent dullness and diminished breath sounds in the right chest. A roentgenogram taken on October 24, 1952, showed the cyst-like area to be absent.

Case No. 3

A seven-month-old white female was admitted to the Children's Hospital on February 1, 1945, with a history of coryza, cough, and fever for 3 days during which time the respirations became grunting in type. She was taken to a suburban hospital where a diagnosis of pneumonia was made, the treatment consisting of penicillin, sulfadiazine, and oxygen. A roentgenogram of the chest was reported as showing "left lung collapsed by air film around the left lung." The patient's condition became worse and she was brought to The Children's Hospital. The past medical history and family history were essentially negative. The usual immunizations had never been carried out.

Physical examination revealed a well-developed white female who appeared acutely ill and somewhat cyanotic and was having labored respirations. The tonsils and pharynx were injected but no exudate was present. There was hyperresonance with distant breath sounds and diminished vocal resonance over the entire left chest which also manifested a respiratory lag.

That evening a thoracentesis was performed and 40 ml. of air was withdrawn along with 2 ml. of thick purulent material. The culture was sterile.

The clinical course of the child was satisfactory. Following the administration of oxygen and antibiotics the temperature returned to normal and all signs of respiratory distress disappeared. The patient was discharged on March 4, 1945.

A roentgenogram taken February 2, 1945, revealed multiple variable sized cystic areas in the upper three quarters of the left lung. The findings eight months later were normal, as well as in 1950.

Case No. 4

B. W., a nine-month-old colored male, was well until three weeks prior to admission when he developed a fever, slight cough, and dyspnea. He was treated in another hospital for several days with penicillin, being released on October 8, 1949, to be admitted to the Children's Hospital because of "lung disease."

Examination revealed a well developed, well nourished colored male in no distress. The temperature was 100.4°, pulse 120. There was some dullness in the right lung posteriorly with diminished breath sounds in this region, No rales were heard.

Chest roentgenogram on October 8, 1949, revealed an opacity over the entire right lung, with displacement of the heart and great vessels to the left. There were several circumscribed areas of decreased density in the right chest. This was thought to represent fluid and some emphysematous blebs.

Penicillin was administered. There were no signs of respiratory distress until 10 days later when the temperature rose to 105.0°. Rales, decreased breath sounds, and a pleural rub were heard over the right lateral chest. A chest roentgenogram at this time revealed essentially the same picture as at admission, with multiple circumscribed areas of pneumothorax, and thickening of the pleura over the apex and peripheral third of the right lung field.

The condition of the child improved. Bronchograms were attempted twice without success. Re-examination of the chest on November 7, 1949, revealed multiple cysts,

with a large one containing fluid in the right chest. There was some improvement roentgenologically.

Follow-up films of the chest two weeks later showed that the multiple cysts had not disappeared. However, one large cyst, 3 x 1.8 centimeters, having a thick fibrotic wall, was still present. Except for brief periods of dyspnea, the child remained asymptomatic. About two weeks later only some irregular areas of thickened pleura in the right lung field remained. Evidence of cystic disease had disappeared and the child continued to do well thereafter.

DISCUSSION

Caffey[1] stresses the importance of "watchful waiting" in the treatment of lung cysts. In addition he points out the desirability of an opinion being rendered by one who is familiar with such findings in young patients, in determining when surgery is to be undertaken.

The lung cysts with cavities may be (1) congenital or may be due to (2) check valve bronchial obstruction, (3) pulmonary infection—bacterial or fungal infection, (4) echinococcus disease or (5) trauma. Other massive obstructive emphysematous lesions, which may be lobar or localized, have been reported[2, 3, 4, 5] as due to (1) chondromalacia with poor bronchial cartilaginous rings which are responsible for an expiratory collapse of the involved bronchi, (2) aberrant veins, (3) patent ductus arteriosus and (4) undetermined cause. Except for two cases cited by Caffey[1] all these patients have come to surgery.

Regional obstructive emphysema[6], which is probably the most common phenomena to occur of all the lesions mentioned above, is seen early in the course of respiratory infections. Undoubtedly many cases are missed because the clinical course may be benign and as a result roentgenograms are not taken. If, during the course of a pulmonary infection, a sufficiently tenacious and copious secretion is present so as to produce an effective occlusion to expiratory forces, and to the alvolar pores of Konh, obstructive emphysema will occur. If the inflammatory exudate persists an air-fluid level will be seen on roentgenogram. Characteristically, these lesions, if followed closely, will fluctuate rapidly in size and shape, becoming larger and after having almost completely disappeared may reappear. One of the authors (S. R.) has observed a patient in whom a "doughnut" lesion appeared and disappeared within a matter of two hours. In Caffey's series[1] he presents the records of patients who not only had single cavities but also multiple ones, with and without air fluid levels.

In one of the patients in our series the cavity developed at a time when the patient was asymptomatic. It was notable that the clinical symptomatology did not correlate with the size of the cavity which fluctuated greatly and seemed to have undergone secondary enlargement before regression.

Characteristically the clinical picture of emphysematous lesions which

have been reported in relation to their surgical treatment, is that of a previously well infant, who develops respiratory symptoms unrelated to a febrile pulmonary process and presents a roentgenogram showing an area of over-aeration and distension with mediastinal shift and other significant signs of emphysema. The etiological factors have already been mentioned.

In a recent report by Kanof[7] et al, on staphylococcal pneumonia, the significant features of this type of pneumonic condition are listed. According to the authors the combination of parenchymal infiltration with atelectasis, abscess formation, empyema, pyopneumothorax, and bleb formation constitutes a unique picture especially when it occurs in the first two months of life. The intrapulmonary abscesses as a rule were multiple, and of variable size. Emphysematous blebs developed in 10 of the 41 cases. It was noted that the appearance could not be correlated with any change in the clinical condition, and that the differentiation from an abscess is difficult. However, the emphysematous areas were observed later in the disease process, usually during the recovery phase.

SUMMARY

These four patients all present a typical picture of a febrile upper respiratory illness with lung involvement and the development of "cyst"-like areas in the lungs, which persisted during the asymptomatic phase of the patients' illnesses. All of these patients were under one year of age at the time of onset. We believe that the persistent cystic areas represent regional obstructions as outlined by Caffey.

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PYRIBENZAMINE INTOXICATION

Case Report No. 271

John D. Bunce, M.D.
Carolyn P. Huntley, M.D.

INTRODUCTION

This case is being presented because the antihistaminic drugs are in such widespread use today and a report of a case showing what was most probably an unusual and serious toxic reaction to pyribenzamine would be of value.

CASE PRESENTATION

J. E. T., a six-year-old colored female was admitted to the Children's Hospital on March 2, 1953. The patient had been well until two days prior to admission at which time she developed a fever of unknown degree, became listless, and ate poorly. She was seen by a physician who made the diagnosis of "flu" and prescribed aspirin and pyribenzamine.

Through a misunderstanding the patient was given 50 milligrams of pyribenzamine every three hours, and for the twenty-four hour period prior to admission the patient received a total of 400 milligrams of pyribenzamine.

During the twelve hour period before admission the patient became very lethargic, stared vacantly into space and refused to talk.

For two months the patient had been treated for a pustular eruption over the legs with penicillin parenterally and local ointments. The past history was otherwise unremarkable.

The patient's parents were apparently well. There was no family history of epilepsy.

The physical examination revealed a well-developed and well-nourished colored female who was semi-conscious. She was sitting quietly in bed staring vacantly. She was unable to stand. Her temperature was 99.4 F.; the pulse rate was 80; the respiratory rate was 20; and the blood pressure was 100/65. The skin was not remarkably dry and was normal except for a sub-acute appearing thick yellow crusted area over the anterior surface of both lower legs. There was no abnormal odor to the breath. The pupils were round, equal and reacted to sustained light. Examination of the fundi was normal. The neck was supple. Examination of the ears, nose, and throat was negative. No abnormality of the cardiorespiratory system was discerned. Examination of the abdomen was negative. Neurologically, the patient was semi-conscious but was easily aroused. She was able to sit but would not stand. She refused to talk but vocalized when given painful stimulus. No cranial nerve involvement was apparent. All the deep tendon reflexes were bilaterally equal.

The diagnosis on admission was encephalitis.

A lumbar puncture was done on admission but was traumatic. The fluid obtained was hazy and contained 29 white blood cells with a differential of 78 lymphocytes and 22 polymorphonuclear cells. It also contained 14.520 red blood cells. Spinal fluid sugar content was 45 milligrams per cent and protein content was 60 milligrams per cent. A cisternal puncture was done about 31 hours later and clear fluid was ob-

tained. The total cell count of the cisternal fluid was 3 white blood cells. The protein content was 14 milligrams per cent and the sugar content was 90 milligrams per cent. The blood sugar on admission was 90 milligrams per cent and the blood urea nitrogen was 11.5 milligrams per cent. A complete blood count, urinalysis, and sickle-cell preparation were normal on admission. A teleroentgenogram taken on the day of admission was normal.

The patient continued to be very drowsy and slept most of the time but tossed constantly while she slept. She refused to take fluids and was very uncooperative when awakened. She continued this way and was kept on a continuous intravenous infusion of 5 per cent glucose in distilled water until the third hospital day when she began having periods of partial lucidity and started taking fluids by mouth. During the third hospital day she gradually became more cooperative and coherent. On the fourth hospital day she was alert, cooperative, and normally active, taking a regular diet. She was discharged to her mother on the fifth hospital day. The pyoderma on the anterior surface of both lower legs was treated with Bacitracin ointment locally starting on the third hospital day and showed considerable improvement at the time of discharge.

DISCUSSION

Because of their effectiveness in the treatment of allergic conditions, the anti-histaminic drugs are in widespread use today. The two most widely used of these drugs are benadryl and pyribenzamine, both of which are complex chemical structures involving benzene rings and possessing similar pharmacologic properties. Pharmacologic studies indicate that these drugs have three important actions: they alleviate: 1) smooth muscle spasm, 2) bronchial constriction caused by histamine or anaphylactic shock and 3) vasodepressor effects of histamine.

There have been many case reports of side reactions to anti-histaminic drugs. Characteristically, these seem to affect the higher brain centers. By far the commonest side reaction is drowsiness, followed by dizziness, tinnitus, weakness, dilated pupils, and dry mouth. Less common reactions are nausea, vomiting, headache and incoordination.

Friedlander reports that pyribenzamine in large doses produces signs of cerebral stimulation as frequently as drowsiness and lassitude. Ratner noted an aggravation of asthma in three per cent of a series and makes the statement that benadryl and pyribenzamine are as dangerous as morphine to an asthmatic since these drugs can dry up bronchial secretions, produce suffocation and can kill a patient in status asthmaticus.

Temporary granulocytopenia has been reported due to pyribenzamine but this complication is extremely rare. Drowsiness has been described in breast fed infants whose mothers had been taking usual doses of antihistaminics.

Irrational and psychotic behavior has been described but this is usually very temporary and stops very shortly after the withdrawal of the drug. The case described in the present article corresponds to those cases in which

there is marked cerebral stimulation and profound irrational and psychotic behavior.

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CLINICO-PATHOLOGICAL CONFERENCE

Directed by: E. Clarence Rice, M.D.
Assisted by: June Pollack, M.D.
By Invitation: Thomas Bradley, M.D.

First admission:

A nine-year-old white female was admitted for biopsy of enlarged cervical lymph nodes.

Three years previously she had mumps and whooping cough. Following recovery from these illnesses, cervical lymphadenopathy persisted. X-ray examination of the chest one month prior to entry revealed miliary lesions throughout both lungs, suggestive of a tuberculous infection. The mediastinal lymph nodes in the hilar region were enlarged. A calcified deposit was seen in the right cervical region of the neck. Roentgenological interpretation favored miliary tuberculosis, but could not exclude a fungus infection or Boeck's sarcoid. Re-examination, two weeks prior to entry, revealed no change from the previous x-ray findings. Films of the skull, abdomen and hands revealed no abnormalities.

Biopsy of a cervical node was done and the child discharged. The pathologist reported that no lymph node was seen in the biopsy section. It revealed dense fibrosis in which were embedded a number of gland spaces which were irregular in pattern and which were lined by well differentiated cuboidal cells. He stated that it was evidently associated with a chronic inflammatory process and that both sarcoid and a metastatic or multicentric growth of the cervical lesion must be considered.

Blood chemistry during hospitalization showed an A/G ratio of 1:1.27, and a blood cholesterol of 150 mgs/100 ml.

Roentgenogram 18 months after discharge revealed no essential change in the chest lesions. Examination of the cervical spine in the AP position disclosed a large

mass in the right cervical region which displaced the trachea to the left and also compressed it somewhat. The same findings were observed 6 months later.

Final admission:

At the age of 11½ years, the child was readmitted with the chief complaint of difficulty in breathing and cyanosis.

Four months prior to admission she had scarlet fever, following which dyspnea and cyanosis occurred intermittently and became progressively more severe. The cervical lymph nodes on the right began to enlarge further, necessitating the use of two pillows at night to relieve dyspnea.

On admission the child was breathing with difficulty through her mouth at the rate of 24 respirations per minute, each breath producing "sucking" sound. Her temperature was 99.8° and the pulse rate was 136 and regular. The pharynx was slightly injected. The right anterior cervical lymph nodes were enlarged and soft. Bronchovesicular breath sounds were heard on examination of the right chest, and both dry and moist rales, chiefly inspiratory, were audible anteriorly and posteriorly. No other significant physical findings were elicited.

Blood examination revealed: Erythrocytes 4,000,000; hemoglobin 12.5 grams; leukocytes 7,600; polymorphonuclear neutrophiles 60 per cent; eosinophiles 2 per cent; lymphocytes 34 per cent, and monocytes 4 per cent. There was no coagulation defect.

Urine: Specific gravity 1.018, acetone present, but normal otherwise.

The immediate post-operative condition was fair with slow recovery from anesthesia. Three hours after operation the child was alert and requested that the tracheal catheter be removed. This was done, and within a few minutes respiratory difficulty ensued. The respirations became rapid, and the pulse rapid and weak. Within about fifteen minutes, respirations ceased. Artificial respiration was ineffectual and the child died approximately four hours post-operatively.

DISCUSSION

Thomas Bradley, M.D.

After reading the entire case history, it is obvious that the diagnosis rests on the cause of the enlarged cervical lymph nodes. The clinical course rules out the ordinary types of cervical adenitis seen in children such as those due to infections, tonsillitis, etc. Enlargement of cervical lymph nodes, which is progressive and eventually fatal, immediately suggests some type of malignancy such as Hodgkin's disease or lymphosarcoma. Tuberculous cervical lymph adenitis usually is not fatal and does not run a course such as this. Among rarer lesions would be actinomycosis, carcinoma of the thyroid, Boeck's sarcoid or perhaps malignant tumor of the parotid gland.

The x-ray of the chest one month prior to entry certainly resembles miliary tuberculosis but the subsequent course of this particular case would tend to rule out tuberculosis. Enlarged mediastinal nodes in the hilar region would suggest Hodgkin's disease of the lungs which can present itself in three ways: first, there may be peribronchial lymph node enlargement, or second, there may be diffuse nodules of varying sizes, such as seen in this case in the lungs, or third, there might be consolidation of a whole

lobe. A tumor of the mediastinum with metastases to the lungs and cervical nodes should be thought of.

The finding of a calcified deposit in the right cervical region is of interest. Brenneman's "System of Pediatrics", chapter 19, page 21, states: "Demonstration of the calcium deposit on x-ray of the neck is quite as conclusive as biopsy in recognition of tuberculous cervical adenitis." I have recently had a case of carcinoma of the thyroid in a child in which calcification of the thyroid was present, so that I do not agree with this statement. Calcification certainly does not occur in Hodgkin's disease nor in Boeck's sarcoid, but could occur in tuberculous cervical lymph adenitis or carcinoma of the thyroid. Reexamination of the chest two weeks after the first film showed no change which would mitigate against a diagnosis of miliary tuberculosis but would be suggestive of metastatic tumor, Hodgkin's disease or perhaps histoplasmosis. Films of the skull, abdomen and hands were all negative. I imagine that the clinician handling the case was trying to demonstrate the punched out lesions of the hands seen in Boeck's sarcoid. Blood chemistry during hospitalization showed an A/G ratio of 1:1.27 and a blood cholesterol of 150 mgm per cent, which I believe are of no diagnostic value. In Boeck's sarcoid the total serum protein is increased due to an elevation of globulin fraction. This hyperglobulinemia causes a reversal of the normal A/G ratio but in the absence of a total protein determination, I do not believe the test is of value. Biopsy report actually represents four possibilities. In essence, it states that it could be an inflammatory process, that it might be Boeck's sarcoid or a metastatic tumor or a multicentric growth. The dense fibrosis is difficult to explain. There is one statement, however, that to my mind is of the utmost importance and that is there were seen glandular spaces lined by well differentiated cuboidal cells. This finding would certainly rule out tuberculosis and sarcoid as such cuboidal cells would not be seen in either disease. Furthermore, Hodgkin's disease or lymphosarcoma produce lesions which superficially do resemble lymph nodes on microscopic examination. Clinically enlarged cervical lymph nodes due to Hodgkin's disease present as freely movable rounded, painless lumps which readily shell out on biopsy. The removal of one of these lumps is quite simple. Tuberculous nodes at first may be discrete but they tend to mat together and their removal is much more difficult. The lumps due to lymphosarcoma are readily removable and resemble the lumps seen in Hodgkin's disease grossly. Carcinoma of the thyroid tends to mat together or form long chains which may become densely adherent to surrounding structures.

The only tumors that I can think of originating in the neck showing well differentiated cuboidal cells would be carcinoma of the thyroid or perhaps a malignant tumor of the parotid with metastasis. X-ray examination 18

months later again reveals no essential change in the chest. This would be a consistent finding with a metastatic malignant tumor rather than miliary tuberculosis. The finding by x-ray that there was a large mass in the right side of the neck displacing the trachea to the left is not of help in differentiating exactly what kind of a tumor is present. Any tumor lying along the prevertebral muscles will displace midline structures. The esophagus or trachea may be displaced in the chest by neurofibromas or almost any type of tumor occupying this particular spot. In adults one immediately thinks of a thyroid tumor whenever displacement of the cervical or upper thoracic thrachea is seen by x-ray.

The final admission apparently represents progression of this tumor with tracheal obstruction producing a sucking noise on respiration. The hemogram which showed an essentially normal red cell count and normal hemoglobin is of interest. The late stage of any malignant tumor in a patient tends to produce anemia. Hodgkin's disease is notorious for producing marked anemia terminally. It is possible that chronic anoxia could produce an elevated red count and hemoglobin superimposed on the anemia produced by advanced malignancy. The normal white count is not of diagnostic significance although sometimes in the late stages of Hodgkin's disease the eosinophil count rises to very high levels approaching 50–60 per cent. The positive acetone test is found in almost any severe illness in children. Apparently the emergency operation relieved the tracheal obstruction and the untimely removal of the tracheal catheter merely hastened the inevitable.

Now to pick out the best possibility amongst the numerous diagnoses which come to mind, an adequate biopsy is essential. Realizing that hindsight is better than foresight, it would seem that a further biopsy was indicated in this case. I am going to base my final selection of a diagnosis on two features; first, the biopsy which showed glandular spaces lined by cuboidal epithelium. This is highly suggestive of carcinoma of the thyroid. Second, the finding of calcification by x-ray in the cervical region in spite of Brenneman's statement to the contrary, does not prove the diagnosis of tuberculosis of cervical nodes, since in one case which I have had personally, carcinoma of the thyroid did have calcification in it and calcification in thyroid malignancy in adults is not too unusual. My first choice is carcinoma of the thyroid with metastasis to the lungs, my second choice is Hodgkin's disease, and third, lymphosarcoma.

June Pollack, M.D.

The students' diagnoses are as follows:
Histoplasmosis, 4

Lymphosarcoma, 3
Carcinoma of the thyroid, 1
Hodgkin's disease, 1
Thymic adenoma, 1
Boeck's sarcoid, 1

At autopsy the body was that of a well developed poorly nourished white female appearing the stated age of ten years. There was a right supraclavicular collar incision at the site of operation. The mediastinal lymph nodes were slightly enlarged but they showed no abnormalities grossly. The bronchial lymph nodes were markedly enlarged and showed several small grayish tumor masses measuring 2–3 mm in diameter.

There was a firm, whitish fibrous mass closely adherent to the trachea extending from the lower portion of the thyroid cartilage to the fourth tracheal ring and the right side of the trachea and deep cervical tissues. Continuous with this mass there were many small groups of firm, enlarged lymph nodes which grossly had the same structure as the mass above. There was a narrowing of the lumen of the trachea in the region of rings two and three due to compression by the mass. No grossly normal thyroid tissue could be seen.

Both pleural cavities contained a small amount of clear fluid. The right and left lungs were non-crepitant and weighed four and three times heavier than normal, respectively. Both had a pebbled appearance, due to the presence of numerous small whitish-gray-pink hard nodules which studded the surface and could be felt throughout the parenchyma, giving the sensation of feeling an overloaded bag of shot. Cut section showed that their presence were sufficiently numerous as to have reduced the amount of functioning pulmonary tissue. The central portions of some of the tumors were soft and reddish in color.

The remainder of the organs showed no abnormalities.

Microscopic examination of the tumor mass in the neck revealed fields of dense fibrous tissue invaded by irregular groups and strands of gland structure, generally rather well differentiated. The epithelial cells varied from large clear forms in some areas to solid plaques of cells with more granular cytoplasm, in other areas. In general, the follicles were well developed and were readily recognized. A number of spaces contained material believed to be colloid. Numerous psammoma bodies were seen.

Microscopic examination of the lung tissue revealed an adenomatous structure similar to that described for the material from the neck. There was greater variation in the glandular arrangement in which a distinct papillary and a sometimes cystic pattern was evident.

Some of the lymph nodes were normal microscopically, however, one

contained a plaque of gland tissue which was identical in appearance with the neoplastic structures previously described. A number of psammoma bodies were seen.

The histopathologic diagnosis was adenocarcinoma of the thyroid with metastases to the bronchial lymph nodes and the lungs.

Theodore Winship, M.D.:

There were two errors in the management of this case. The case was not as well investigated as it might have been, and there was not sufficient tissue obtained at biopsy to make an accurate diagnosis. This child might have had a radical removal of the neck tumor and the pulmonary tumors might have been treated with radioactive iodine.

Thyroid carcinoma in children is very similar to that seen in the adult. They may be classified as papillary, follicular and undifferentiated.

There are three forms of surgical treatment used today:

1. Thyroid lobectomy with a radical neck dissection including removal of the sternomastoid muscle and the internal jugular vein.
2. Thyroid lobectomy and removal of one-half of the sternomastoid muscle and as much of the tumor tissue as possible.
3. Hemithyroidectomy with removal of the small nodes in the neck.

Crile is a proponent of the third form of therapy in cases of papillary carcinoma of the thyroid. He believes that the papillary tumors will not invade the neck structures, but I am not in agreement.

Ward performs a lobectomy for all nodules in thyroid gland in children and males and for all single nodules in females.

Fifteen per cent of all thyroid tumors appear as nodules in the neck. The diagnosis is based on biopsy and a histological examination of the tissue.

The treatment of choice is a combined block dissection of the neck and hemithyroidectomy with removal of the isthmus.

Dr. Rice: How common is carcinoma of the thyroid in children?

Dr. Winship: On reviewing the surgical records at Children's Hospital in Washington, D.C., for the past thirty-seven years, there were four cases of carcinoma of the thyroid out of the ten cases operated on and four more cases were treated in other hospitals in the District of Columbia.

It is interesting that there is little correlation between the frequency with which carcinoma of the thyroid is seen in children and the goiter areas of the United States. Los Angeles has reported no cases of cancer of the thyroid in children, but six children with this tumor have been seen in San Francisco. I am convinced that the interest of the physician in thyroid disease determines the frequency with which this malignant tumor will be seen.

Dr. Pollack: What can you say about longevity?

Dr. Winship: Little is known about this. The average follow-up is of little value. Patients with carcinoma of the thyroid live longer than those with cancer arising from other organs. Crile has 12 patients who have lived between 12 and 17 years. The mortality is about 15 per cent. Foot states that 21 per cent of these tumors can be classified as of the papillary type. Fitzgerald reports that 20 per cent of his patients who developed cancer of the thyroid during childhood had received irradiations for the treatment of enlargement of the thymus gland during infancy. Five babies are known to have been born with cancer of the thyroid gland.

Dr. Guin: Have any giant cell tumors been reported?

Dr. Winship: One giant cell carcinoma and three Hurthle cell carcinoma have been.

Student: What in this case led you to make the diagnosis of carcinoma of the thyroid?

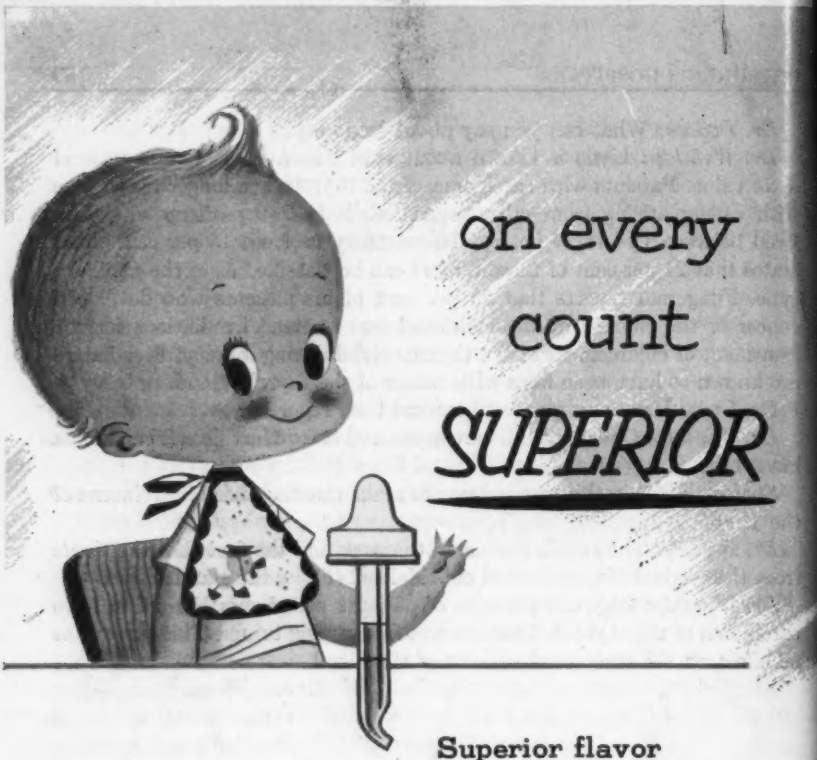
Dr. Bradley: The calcified areas in the neck and the fact that the tissue from the original biopsy showed cuboidal cells lining the gland spaces.

Dr. Winship: Only one per cent of patients with hyperthyroidism have carcinoma of the thyroid. This is a non-functioning tumor. This tumor has no effect on the cholesterol content of the blood.

DR. BLAIR APPOINTED

Dr. Montgomery Blair, medical director of The Children's Hospital, Washington, D. C., has been named as the ninth member of the new District of Columbia Public Welfare Advisory Council. His appointment by the District Commissioners completes membership of the Council, which was set up in July after the Board of Public Welfare was eliminated as part of a reorganization plan.

Dr. Blair is on the consulting staff at Garfield Hospital and on the medical advisory board of Christ Child Convalescent Home in Rockville, Md. He is also on the medical advisory committee of the District Chapter National Foundation for Infantile Paralysis.



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